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A novel approach to the regioselective acylation of spirocyclic *C*-glucoside of papulacandins

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Abstract—A novel approach to the regioselective acylation of spirocyclic *C*-glucoside of papulacandins is reported. Conditions were found to effect regioselective acylation of triol **2** to give 2-*O*-acyl derivatives (**5**), which after deprotection with TASF afforded exclusively 2-*O*-acyl derivatives (**8**). An extensive migration of the acyl group from 2-*O*- to 3-*O*-position was observed when the desilylation was conducted with TBAF. These findings provided with a convenient means for extending the SAR of papulacandins at these positions.

In 1977, Traxler and co-workers reported the isolation and characterization of a family of novel antifungal antibiotics, named papulacandins A, B, C and D from *Papularia sphaerospema*,[1–3] with in vitro activity against *Candida albicans* and other yeasts. In general these compounds showed acceptable inhibition of β-1,3-glucan synthase and whole cell activity, though little or no efficacy in animal models was found.

The papulacandins A, B and C contain a spirocyclic diglycoside and two unsaturated fatty acids, linked as esters to two hydroxyl groups of the diglycosides. Papulacandin D, a monosaccharide relative is the simplest member of the family.[4] The antifungal properties of papulacandin D juxtaposed with lack of access to natural material and the synthetically challenging structural features make this compound interesting synthetic target.[5–11]

While the construction of the spirocyclic *C*-aryl glucoside moiety of papulacandin D has been widely documented, there is only one report that describes a

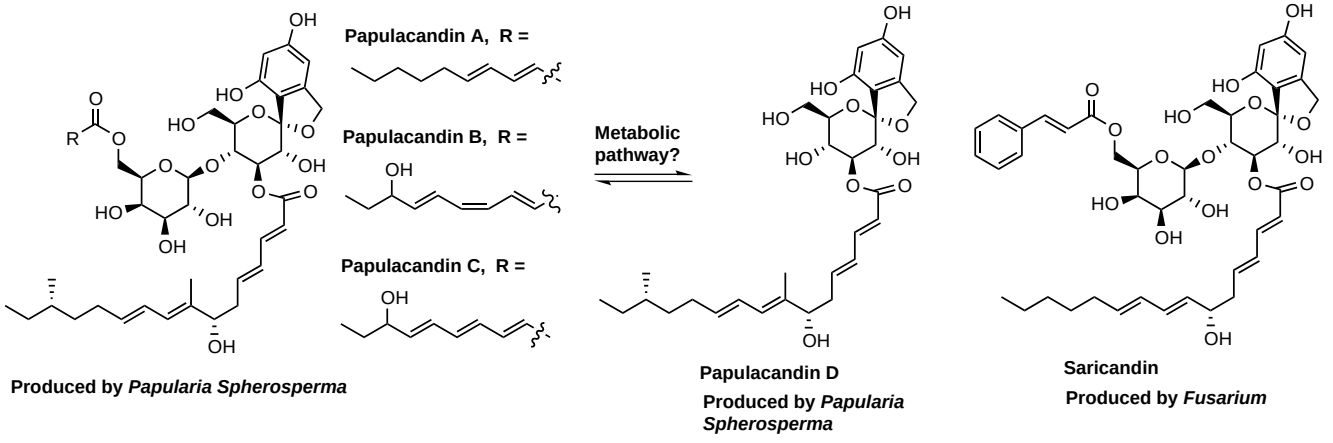

Figure 1. Members of the papulacandins family.

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successful attempt to address the incorporation of the side chain.[11] The main challenge in conducting an SAR to improve the in vivo profile of these class of antifungal agents is the regioselectivity of the acylation. Barrett has reported the use of the mixed anhydride in combination with *O*-4″,*O*-6″-di-*tert*-butylsilylene and triisopropylsilyl protecting groups as a way of improving the reactivity and regioselectivity. We recently applied this combination of protecting groups to realize the total synthesis of a saricandin analog (Fig. 1) corresponding to papulacandin D.[12] The use of protecting groups such as di-*t*-butylsilyl(trifluoromethanesulfonate) makes the development of analogues quite expensive. Moreover, only a modest regioselectivty (3:1) and modest yield (31%) were achieved.

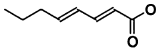
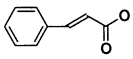
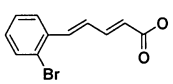
We now wish to report a novel approach to the regioselective acylation of spirocyclic *C*-glycoside that permitted to extend the SAR at *O*-2 and *O*-3 position of papulacandin D.

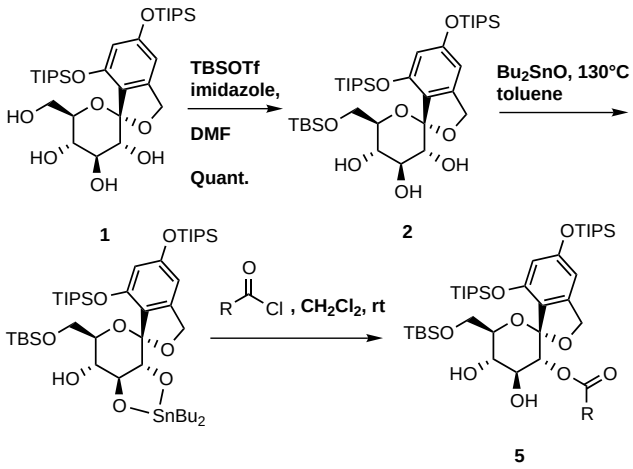
For the synthesis of the tricyclic spiroketal nucleus **1** we used reaction sequences analogous to that described by Barrett for the synthesis of papulacandin D.[5] Our strategy begins with a selective silylation of the primary hydroxyl group of **1** that afforded cleanly 6-*O*-silyl derivative **2**. Representative examples of unsaturated side chains of interest for the SAR were selected for the present studies (Table 1).

The direct acylation of **2** with either acyl chlorides or mixed anhydrides led to a mixture of several products. However, we were pleased to find that activation of the 2,3-diol with dibutyltin oxide prior to the reaction with acyl chlorides[13] gave the 2-*O*-acyl derivative **5** as the sole product[14] (see Scheme 1 and Table 1). Presumably, the oxygen atom of the spiroketal moiety is responsible for the regioselectivity of the reaction. Surprisingly, when bis(tributyltin oxide) was used as the promoter,[13] no reaction was obtained, and starting material was recovered unaltered.

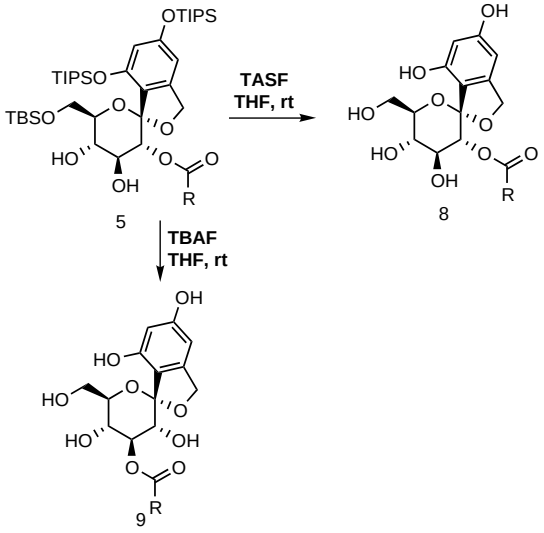
Next, we studied the deprotection of ester **5** (see Scheme 2 and Table 2).[15] When the esters **5** were subjected to deprotection with tris(dimethylamino)-sulfur (trimethylsilyl)difluoride (TAS-F),[11] the sole

Table 1.

Compound	R	Yield (%)
5a		64
5b		77
5c		48
5d		75



Scheme 1.



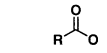
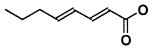
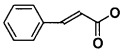
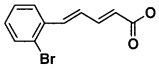
Scheme 2.

products formed and isolated in a good yield were the corresponding polyols **8**. Interestingly, we found (partly by chance!) that the deprotection of **5** with tetrabutylammonium fluoride (TBAF) was accompanied by an extensive migration of the acyl group from 2-*O*- to 3-*O*-position leading predominantly to the polyols **9**. These findings provided with a convenient means for extending the SAR of papulacandin at these strategic positions.

We investigated the scope of the migration reaction and found that it was limited to the preparation of α,β-unsaturated esters. Attempts to apply to saturated esters or phenyl ester resulted in much lesser extent of migration when treated with TBAF.

In summary, conditions were found to affect regioselective acylation of triol **2** to give 2-*O*-acyl derivatives (**5**), which after deprotection with TASF afforded exclusively 2-*O*- acyl derivatives (**8**). A extensive migration of the acyl group from 2-*O*- to 3-*O*-position was observed when the desilylation was conducted with

Table 2.

Compound		Deprotection of **5** with TBAF: Yield (%) **(8 : 9)**	Deprotection of **5** with TASF: Yield (%) **(8 : 9)**
8a, 9a		72 (15 : 85)	86 (100 : 0)
8b, 9b		86 (19 : 81)	90 (100 : 0)
8c, 9c		69 (19 : 81)	85 (100 : 0)

TBAF. These findings provided with a convenient mean for extending the SAR of papulacandin at these postions.

Acknowledgements

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References

1. Traxler, P.; Gruner, J.; Auden, J. A. L. *J. Antibiot*. **1977**, *30*, 289–296.
2. Traxler, P.; Fritz, H.; Richter, W. J. *Helv. Chim. Acta* **1977**, *60*, 578–584.
3. Traxler, P.; Fritz, H.; Fuhrer, H.; Richter, W. J. *J. Antibiot*. **1980**, *33*, 967–978.
4. For a review on *C*-aryl glycosides, see: Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1–20.
5. Danishefsky, S.; Phillips, G.; Ciufolini, M. *Carbohydr. Res*. **1987**, *171*, 317–327.
6. Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163–7169.
7. Friesen, R. W.; Sturino, C. F. *J. Org. Chem*. **1990**, *55*, 5808–5810.
8. Dubois, E.; Beau, J.-M. *Carbohydr. Res*. **1992**, *223*, 157–167.
9. Rosenblum, S. B.; Bihovsky, R. *J. Am. Chem. Soc*. **1990**, *112*, 2746–2748.
10. Czernecki, S.; Perlat, M.-C. *J. Org. Chem*. **1991**, *56*, 6289–6292.
11. Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem*. **1996**, *61*, 1082–1100.
12. Hamdouchi, C.; Sanchez, C. *Synthesis* **2001**, 833.
13. David, S. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp. 69–83.
14. Experimental procedure: A solution of the corresponding acid (0.500 mmol) in dichloromethane (5 mL) was treated under N_2 with oxalyl chloride (2 M in dichloromethane, 2.0 equiv.) and DMF (0.10 equiv.) at 0°C. After 1 h, the solvent was removed in vacuo under N_2, and dichloromethane (5 mL) was added. The resulting solution (ca. 1.2 equiv.) was added under N_2 to a solution of 2 (0.402) in toluene (5 mL) which had been treated, in the presence of 4 Å molecular sieves (500 mg) with Bu_2SnO (1.0 equiv.) at 130°C for 20 h and then cooled to rt. When the reaction was judged complete by TLC, the mixture was filtered through a pad of Celite and concentrated in vacuo. Compounds **5a–d** were purified by flash chromatography (eluent:hexanes/EtOAc). All new compounds gave satisfactory elemental analyses, ^1H and ^{13}C NMR spectra.
15. Compound **5a**: oil; $[\alpha]_D$ –57.7° (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.04–6.91 (m, 1H, =CH), 6.28 (d, $J=1.5$, 1H, ArH), 6.18 (d, $J=1.5$, 1H, ArH), 6.03–6.00 (m, 2H, 2=CH), 5.62 (d, $J=10.0$, 1H, H–2), 5.54 (d, $J=15.1$, 1H,=CH), 5.12 (d, $J=12.6$, 1H, ArCH), 5.07 (d, $J=12.6$, 1H, ArCH), 4.14–3.61 (m, 5H, H-3, H-4, H-5, H-6a, H-6b), 2.94 (d, $J=4.3$, 1H, OH), 2.09 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.35–1.03 (m, 42H, 6 $(CH_3)_2CH$ and 6 $(CH_3)_2CH$), 0.88 (t, 3H, CH_3), 0.87 (s, 9 H, $(CH_3)_3C$), 0.05 (s, 3H, CH_3Si), and 0.03 (s, 3H, CH_3Si); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.4, 158.6, 152.3, 145.8, 144.7, 143.3, 128.4, 118.7, 118.3, 109.4, 109.1, 104.5, 75.2, 73.9, 73.8, 72.9, 71.6, 65.6, 34.9, 29.7, 25.8, 21.8, 18.1, 17.8, 13.6, 13.1, 12.5, –5.5, and –5.7; HRMS (FAB+) 849.516593 (calcd for $C_{45}H_{81}O_9Si_3$ 849.518845)
Compound **8a**: mp >135°C (dec.); $[\alpha]_D$ –44.4° (*c* 1.0, CH_3OH); ^1H NMR (CD_3OD, 200 MHz) δ 7.12–6.99 (m, 1H,=CH), 6.21–6.08 (m, 4H, 2 ArH and 2=CH), 5.63 (d, $J=9.8$, 1H, H-2), 5.61 (d, $J=15.8$, 1H,=CH), 5.05 (d, $J=12.6$, 1H, ArCH), 4.95 (d, $J=12.6$, 1H, ArCH), 3.92 (dd, $J=9.1$, 9.7, 1H, H-3), 3.86 (ddd, $J=2.3$, 2.4, 9.7, 1H, H-5), 3.79–3.76 (m, 2H, H-6a, H-6b), 3.64 (dd, $J=9.2$, 9.6, 1H, H-4), 2.12 (ddd, $J=5.4$, 7.1, 7.4, 2H, CH_2), 1.42 (ddq, $J=7.1$, 7.4, 7.4, 2H, CH_2), and 0.90 (t, $J=7.4$, 3H, CH_3); ^{13}C NMR (CD_3OD, 50 MHz) δ 167.8, 161.7, 154.8, 146.6, 145.7, 145.0, 129.8, 119.8, 115.5, 110.7, 103.1, 99.7, 76.1, 74.9, 74.6, 74.0, 71.3, 62.5, 36.0, 23.0, and 14.0; HRMS (FAB+) 423.165610 (calcd for $C_{21}H_{27}O_9$ 423.165508)
Compound **9a**: mp >124°C (dec.); $[\alpha]_D$ +15.3° (*c* 0.5, CH_3OH); ^1H NMR (CD_3OD, 200 MHz) δ 7.32 (dd, $J=10.0$, 15.4, 1H,=CH), 6.34–6.17 (m, 2H, 2=CH), 6.19 (s, 1H, ArH), 6.18 (s, 1H, ArH), 5.91 (d, $J=15.4$,

1H,=CH), 5.34 (dd, $J=9.3$, 10.0, 1H, H-3), 5.06 (d, $J=12.6$, 1H, ArCH), 4.98 (d, $J=12.6$, 1H, ArCH), 4.33 (d, $J=10.0$, 1H, H-2), 3.92–3.59 (m, 4H, H-4, H-5, H-6a, H-6b), 2.17 (ddd, $J=6.1$, 6.9, 7.3, 2H, CH_2), 1.47 (ddq, $J=6.9$, 7.3, 7.5, 2H, CH_2), and 0.93 (t, $J=7.5$, 3H, CH_3); ^{13}C NMR (CD_3OD, 50 MHz) δ 169.1, 161.6, 154.7, 146.7, 145.7, 145.5, 129.9, 120.5, 116.6, 112.1, 102.9, 99.9, 78.3, 75.8, 73.8, 71.9, 69.8, 62.5, 36.0, 23.0, and 14.0; HRMS (FAB+) 423.166496 (calcd for $C_{21}H_{27}O_9$ 423.165508)